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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/988,150
Filing Date: November 19, 2001
Appellant(s): CREMASCHI ET AL.

Daniel J. Pereira, Ph.D.
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 12-28-2005 appealing from the Office action mailed 03-09-2005.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

There are no related appeals, interferences, and or judicial proceedings known to the examiner which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is incorrect. Claims **12 and 21** (not 20-21) are objected to. This was possibly due to an inadvertent mis-numbering on the Office Action Summary sheet mailed 03-09-2005. However, the mailed Action clearly indicates that claims 12 and 21 were objected to under 37 CFR 1.75(c) on page 2. Further, Appellants correctly note that claims 12 and 21 were objected to in their Brief on page 3. A correct statement of the status of the claims is as follows:

Claims 11-13, 15-22, and 24-28 are pending.

This appeal involves Claims 11-13, and 15-19.

Claims 12 and 21 are objected to.

Claims 20, 22, and 24-28 are allowable.

(4) Status of Amendments After Final

No amendment after final has been filed.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is substantially correct. Appellant's brief presents arguments (page 9) relating to the *objection* of Claims 12 and 21. Hence, Issue 2 of the Brief (page 3) appears to relate to petitionable subject matter under 37 CFR 1.181 and not to appealable subject matter. See MPEP § 1002 and § 1201.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

With regards to Issue I:

- Smith *et al.* (WO 94/28879) December 22, 1994
- U.S. Patent No. 5,879,712 (Bomberger *et al.*, June 1995)
- Almeida *et al.* ("Nasal Delivery of Vaccines", Jnl. of Drug Targeting, 1996, Vol. 3, pages 455-467.

With regards to Issue 2, the evidence relied upon includes definitions of "protein" and "polypeptide" from Zaid et al. "Glossary of biotechnology and genetic engineering" FAO Research & Technology Paper, No. 7, 1999, pp. 183, 190.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

(i) Claims 11-13, and 15-19 are rejected under 35 USC 103(a) as being unpatentable over Smith *et al.* (WO94/28879, IDS) in view of U.S. Patent No. 5,879,712 (Bomberger *et al.*, June 1995) and Almeida *et al.* ("Nasal Delivery of Vaccines", Jnl. of Drug Targeting, 1996, Vol. 3, pages 455-467.

(ii) Smith *et al.* is the primary reference and teaches all of the limitations of Claims 11-13 and 15-19 except Smith *et al.* does not teach "intranasal" administration of the polypeptide. Smith teaches a method for administering a composition comprising a microparticle having a protein and an antibody adsorbed thereon, wherein said administering comprises contacting a microparticle having a protein and an antibody thereon for oral administration (see abstract); wherein said protein is selected from the group consisting of BSA, insulin, enkephalin, hormones, growth factors, cytokines, coagulation factors, polypeptides, and antimicrobial agents (see page 6); wherein said antibody is an immunoglobulin selected from the group consisting of IgM, IgA, and IgG (see page 3); wherein said immunoglobulin is specific for the protein (see page 4) wherein said microparticle is biodegradable (see page 7); wherein said microparticle comprises polystyrene (see page 8); wherein the ratio of protein to

antibody is 1 to 15, 000, 1 to 5000, or 1 to 100 moles of protein per mole of antibody (see page 19).

(iii) The secondary references of Bomberger *et al.* and Almeida *et al.* provide the requisite motivation to include intranasal administration because Bomberger *et al.* teach the intranasal administration of microparticles loaded with biologically active drugs, including proteins such as ICAM-1 (abstract, column 1, lines 20+, column 4, lines 45+). Further, Almeida *et al* teach that microparticles can act as carriers for antigens delivered by the nasal route (page 462, 2nd column, page 463, 1st column). Almeida *et al.* further teach that "intranasal immunization appears the *superior* route to achieve a comprehensive immune response" wherein the advantages of nasal delivered medicines (compared to other mucosal surfaces) include the valuable mucosal surface of approximately 150 cm^2, the accessibility and easy administration that increases patient compliance, and a highly vascularized and venous flow that escapes the portal system, thus preventing first-pass metabolism in the liver (page 457, 1st column).

Hence, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to include nasal administration of the composition taught by Smith *et al.* because nasal administration of microparticles containing peptides and proteins was well established in the art as taught by Bomberger *et al.* (US Patent No. 5,879,712) Further, one would have been motivated to do so because Almeida *et al.* teach that nasal delivered vaccines are advantageous compared to other mucosal surfaces because of the valuable surface area of the nasal mucosa, the easier accessibility and administration that

increases patient compliance, and a highly vascularized and venous flow that bypasses the portal system, thus preventing first-pass metabolism in the liver (page 457, 1st column). Thus, given the state of the art, success, and advantages of intranasal administration of microparticles, it would have been obvious to include nasal delivery of the claimed compound, and one of ordinary skill in the art would have a reasonable expectation of success in administering the claimed compound via the nasal passageway.

(10) Response to Argument

Issue #1:

Appellants argue (Brief, page 4) that the claimed invention is not obvious for two reasons. First, appellants argue that the combination of Smith, Bomberger, and Almeida do not provide the requisite motivation to perform the claimed method, i.e., intranasal administration of the composition comprising a microparticle having protein and antibody adsorbed thereon as required in Claim 1.

Secondly, appellants argue that the combination of cited prior art provide no suggestion or reasonable expectation for the vast improvement for the delivery of the composition defined in "Claim 11" when delivered through the nasasl mucosa relative to the intestinal mucosa, which data are of record in the present application.

With regards to the first argument, Appellants argue that the suggested advantages of nasal delivery as cited in Bomberger *et al.* and Almeida *et al.* is untenable. In particular, appellants point out (top of Brief, page 5) that while Almeida describes several advantages of

administering drugs nasally, a latter passage in the same reference (page 461, 2nd column, second paragraph) suggests that the adsorption through the intestinal and nasal mucosa are similar. With regards to Bomberger, appellants argue that their teachings fail to provide "any disclosure relevant" to the obviousness of the claimed invention. Appellants point out that while Bomberger describes microparticles having controlled degradation particles for the controlled delivery of drugs to the nasal passageway, the reference (throughout its disclosure) teaches that the drug to be delivered is contained within the microparticle (column 15, lines 29-31). In contrast, appellants argue that the claimed composition has a protein and antibody adsorbed onto the microparticle NOT encapsulated within the microparticle as taught by Bomberger.

Thus, appellants argue (Brief, bottom of page 5) that the motivation to administer the Smith composition intranasally is based either on hindsight reconstruction or under an obvious to try rationale.

These arguments have been carefully considered but are not found persuasive. First, at the time the present invention was filed the teachings of both Bomberger and Almeida evidence that intranasal delivery was a well-recognized route of microparticle vaccine administration. Secondly, Almeida expressly teaches the superior advantages associated with intranasal administration (Almeida, page 457, column 1). As noted in MPEP §2144, the expectation of some advantage is the strongest rationale for combining references. (The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. *In re Sernaker*, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983).)

In contrast, Appellants appear to suggest that Almeida lacks the requisite motivation (or provides a teaching away) from nasal administration of the claimed composition because there is a suggestion in Almeida that the "mechanism" of solid particle uptake by the nasal mucosa is *similar* to that found in the gut. However, appellants fail to clarify why or how this mechanism constitutes a teaching away from the broader teachings of Almeida. Also, the epithelial cells lining the intestine and the epithelial cells lining the nasal mucosa may participate in solid particle uptake in the same fashion, but there is no evidence to suggest that this mechanism negatively effects the volume or flow of material transported across the epithelium.

In regard to appellant's discussion of Bomberger's disclosure, appellants similarly fail to explain why one of ordinary skill in the art would regard intranasal administration of the drug encapsulated "within a microparticle" a significant teaching away from the claimed composition. Moreover, the passage (col. 15, lines 29-31) to which Appellants refer to in Bomberger does not appear to expressly teach that the drug is necessarily encapsulated within the microparticle:

> "The drug-loaded microparticles produced in accordance with the present invention have the properties of adhering to the nasal passageway, and gradually releasing the drug contained therewithin into the circulatory system of the recipient patient. The alginate in the microparticle interacts with the mucosa contained in the nasal passageway to become a gel-like substance which adheres to the surface of the nasal passageway as the drug is released."

On the contrary, Bomberger appears to teach away from microencapsulation because such methods are impractical for commercial production of microparticles containing proteins such as ICAM-1: (see column 3, lines 27+)

> "Although there are several reports of using alginate beads to <u>microencapsulate peptides and proteins</u>, nearly all reports indicate bead sizes over 100 μm in diameter. In addition, nearly all reports prepare alginate gel beads by dropping sodium alginate solution into an

> aqueous calcium chloride solution to form the beads. While such a method does produce microencapsulated beads, the difficulty in controlling operating conditions to produce microparticles in the desired size range, difficulty in scaling, and the lack of suitability to clean pharmaceutical processing makes such methods impractical for commercial production of microparticles containing proteins such as ICAM-1."

Thus, with regards to Appellant's first arguments, it would appear that Appellant has argued and discussed the references individually without clearly addressing the combined teachings. It must be remembered that the references are relied upon in combination and are not meant to be considered separately as in a vacuum. According to the MPEP (§ 2145), one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Appellant's second argument (Brief, page 6) is that the *prima facie* case is rebutted because the specification teaches greater than expected results of microparticle absorption through the nasal mucosa compared to the intestines. Appellants submit that experiments preformed *in vitro* (nasal tissue) at lower than physiological temperatures gave greater than expected results compared to *in vivo* (intestinal mucosa) experiments at physiological temperatures of 37^0C. Further, Appellants submit (Brief, page 7) that comparing *in vitro* nasal mucosa data and *in vivo* intestinal data is appropriate. For adsorption in the intestines, *in vivo*, the proteins are adsorbed by intestinal epithelium at 37^0C, then pass into connective tissue where they then reach the ducts and where the microparticle numbers are measured (Appellant's specification, page 3, lines 20-23). For the nasal mucosa, *in vitro* testing is performed at a lower temperature (27^0C) and consists of a pseudoepithelium layer and a thin layer of connective tissue. Appellants argue (Brief, top of page 7) that as compared with 37^0C, the lower temperature

performed with the nasal mucosa *in vitro* lowers metabolism and transport twice as much, but renders the isolated tissue more stable. Appellants further speculate that since microparticle transport at 27^0C is 400,000 times greater than transport in the intestine at 37^0C, it would be expected that "if the experiments in the nasal mucosa were performed at 37^0C the resulting increase through the nasal mucosa would have been approximately 800,000 times greater than the intestine". These arguments have been carefully considered but are not found wholly persuasive. Clearly there are some transport differences between the two tissues, but it remains unclear why appellant believes the comparison between the *in vivo* conditions versus the *in vitro* conditions is experimentally "appropriate". Appellants only appear to have compared the different methodological procedures while remarking on the different temperature settings. Those of skill in the art recognize that *in vitro* assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However the greatly increased complexity of the *in vivo* environment as compared to the very narrowly defined and controlled conditions of an *in vitro* assay rarely permit extrapolation with any reasonable degree of predictability. Further, the expectation that experiments performed at 37^0C in the nasal mucosa would predictably result in approximately 800,000 times greater transport versus the intestine are not persuasive because, as appellant's note (Brief, page 7, 1st para, last sentence), "the experimental conditions of 27^0C more closely mimic the real temperature of the nasal mucosa in a living individual". Hence, it appears that it would be unscientific to perform these experiments using nasal epithelium at 37^0C.

Assuming the Board does accept Appellant's rationale that comparing *in vitro* nasal mucosa data and *in vivo* intestinal data is appropriate, it must be addressed whether or not the

greater than 400,000 times more microparticles absorbed through the nasal mucosa was greater than expected and/or nonobvious.

To consider that which might be unexpected, there must exist some historical baseline values that help to establish what might normally be expected when microparticles are adsorbed across either intestinal and or nasal mucosal surfaces. Here it is noted that neither Almeida *et al.* nor Bomberger *et al.* report conventional values that measured trans-epithelial transport of microparticles across mucosal surfaces. In regards to Smith (WO 94/28879), the reference established that beads coated with bGH to which a specific antibody is later bound is taken up about ten times more readily than are beads coated with bGH alone (page 14) presented as means +/- SEM estimated over $3x10^4$ μm^2 of intestinal follicle surface. Thus, Smith compared the uptake in the same tissues (intestinal) using different microparticle compositions with no expectation that the microparticles would continue past the M cells into the lymphatic system (Smith, top of page 5). Contrast this with appellants who used the same microparticle compositions in different tissues (nasal vs. intestinal mucosa) with higher results in one tissue versus the other tissue. It is noted that Appellant's specification does not compare these results to any historical perspective and simply states (page 4), "It has now surprisingly been found that yield of active transport in nasal mucous membrane of a protein and the specific antibody of the said substance adsorbed on microparticles of polymeric substance is 400 thousand times higher than that of the intestine". On the other hand, Almeida *et al.* expressly teaches (page 457, 1st column) that "the nasal administration of drugs exploits the higher permeability of the nasal mucosa when compared to other mucosal surfaces". Thus, it would appear that Appellant's higher results in the nasal mucosa would naturally occur by following the suggestive teachings of

the prior art. "The fact that appellant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious." *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985) (The prior art taught combustion fluid analyzers which used labyrinth heaters to maintain the samples at a uniform temperature. Although appellant showed an unexpectedly shorter response time was obtained when a labyrinth heater was employed, the Board held this advantage would flow naturally from following the suggestion of the prior art.). See also *Lantech Inc. v. Kaufman Co. of Ohio Inc.*, 878 F.2d 1446, 12 USPQ2d 1076, 1077 (Fed. Cir. 1989), *cert. denied*, 493 U.S. 1058 (1990) (unpublished - not citable as precedent) ("The recitation of an additional advantage associated with doing what the prior art suggests does not lend patentability to an otherwise unpatentable invention.").

Issue #2:

This issue was not considered because it was not drawn to any rejected claims and therefore was not considered an appealable issue.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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